



## **Technical Memorandum**

### **Comments on Arizona Department of Environmental Quality Ambient Air Criteria for Hazardous Air Pollutants**

Prepared for

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September 2005

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As a part of their development of an air toxics program, the Arizona Department of Environmental Quality (ADEQ) has derived acute and chronic ambient air criteria (AACs) for use in source category listing, determining whether additional controls are necessary (e.g., hazardous air pollutant reasonable available control technology [HAPRACT]), and determining whether source modifications are *de minimis* for needing HAPRACT. The development of these AACs for federal hazardous air pollutants (HAPs) is described in two documents: *Arizona DEQ - Development of Acute Health-Based Ambient Air Criteria* (June 7, 2005) and *Arizona DEQ - Development of Chronic Ambient Air Concentrations (Long Term)* (April 22, 2005) (hereafter referred to as the Acute AAC and Chronic AAC documents). ADEQ has also released a related document describing how ambient air concentrations for facilities will be modeled for comparison to AACs: *Procedure for Ambient Air Quality Dispersion Modeling for the Arizona HAPRACT Rule* (July 5, 2005).

In response to ADEQ's request for stakeholder and public comment, Exponent is providing comments on the AACs. In general, the Acute and Chronic AAC documents reflect thoughtful consideration of existing methodologies for deriving health-based levels and applying them in the state air program. Our primary comment on the process for deriving AACs, as detailed in these two documents, is that the methodology for deriving chronic AACs, in particular, is inconsistent with the definition in the applicable Arizona State statute. Combined with very conservative, worst-case modeling assumptions, receptor location (25 m from the process area), and initial screening criterion for modeled concentrations (80% of the AAC), ADEQ's overall approach is expected to greatly overestimate actual risks of adverse effects, and the approach is inconsistent with applicable statutory language.

According to the statute, a fundamental criterion for determining whether a source category should be listed is whether emissions of hazardous air pollutants "result in adverse effects to human health or adverse effects to the environment" (49-426.05, subsection A). In addition, for facilities that emit more than 1 ton per year of any one HAP, or 2.5 tons per year of any

combination of HAPs but less than 10 tons per year of any one HAP, or 25 tons of any combination of HAPs, a determination as to whether HAPRACT should be required for a new or modified source depends on whether such control is necessary to avoid “adverse effects to human health or adverse environmental effects” (49-426.06, subsection C).

The State statute defines “adverse effects” as follows:

49-401.01, paragraph 2. “‘Adverse effects to human health’ means those effects that result in or significantly contribute to an **increase in mortality** or an **increase in serious irreversible or incapacitating reversible illness** [emphasis added], including adverse effects that are known to be or may reasonably be anticipated to be caused by substances that are acutely toxic, chronically toxic, carcinogenic, mutagenic, teratogenic, neurotoxic or causative of reproductive dysfunction.”

49-401.01, paragraph 3. “‘Adverse environmental effect’ means any significant and widespread adverse effect which may reasonably be anticipated on wildlife, aquatic life, or natural resources, including adverse impacts on populations of endangered or threatened species or significant degradation of environmental quality over broad areas.”

In addition, if ADEQ intends to use their methodology to derive AACs for use in developing a list of state HAPs, the following criteria will have to be met:

- 1) 49-426.04, subsection A, paragraph 1 (a). “There is scientifically reliable evidence on the health or environmental effects of the pollutant adequate to support the designation. The director shall rely on technical protocols appropriate for the development of the list of hazardous air pollutants and shall base the designation on credible medical and toxicological evidence that has been subject to peer review. **Evidence shall be considered scientifically reliable only if it demonstrates adverse effects to human health or adverse environmental effects from an air pollutant at concentrations that are likely to occur in the environment** [emphasis added] as a result of emissions of the pollutant into the ambient air.”

- 2) 49-426.04, subsection A, paragraph 1 (b). “Emissions, ambient concentrations, bioaccumulation or deposition of the **pollutant result in adverse effects to human health or adverse environmental effects**” [emphasis added].
- 3) 49-426.04, subsection A, paragraph 1 (c). “An adequate and reliable methodology exists for quantifying emissions and ambient concentrations of the pollutant.”

In the course of reviewing the approach used to develop health-based chronic AACs, a number of issues were identified. These issues, delineated below, should be addressed to ensure that the methodology reflects the best science and is consistent with the statutory language.

## **The basis for chronic ambient air concentrations is inconsistent with the applicable State statute**

As already discussed, the statute indicates that concentrations must be based on “**adverse effects to human health**” that **result in or significantly contribute to** an increase in mortality, serious irreversible illness, or serious incapacitating reversible illness. The Acute AAC document acknowledges this definition in the introductory section, and the bases of the acute AACs (e.g., EPA Acute Exposure Guideline Level 2) are consistent with this definition. In contrast, the Chronic AAC document states that “Health based chronic ambient air criteria will be developed for individuals (including sensitive populations) to establish exposure levels to protect against serious health effects.” This definition of a chronic AAC is more consistent with that used to describe U.S. Environmental Protection Agency (EPA) reference doses (RfDs) and preliminary remediation goals (PRGs)—values that are set well below no-effects levels by a considerable margin. Because of the many conservative (i.e., tending to overestimate risk) assumptions that are built into these values, RfDs and PRGs often greatly overestimate the actual potential for health effects in humans. As such, these values are not intended to define levels above which adverse effects, as defined by the State statute, would result.

The derivation of the AACs in many cases also is inconsistent with the current scientific evidence for adverse health effects by inhalation. Many of the chronic AACs are based on

extrapolation from oral studies, even though it may not always be appropriate to do so (comments regarding limitations of route-to-route extrapolation follow). Some chronic AACs are based on extrapolation from high-dose laboratory animal data, even when data are available in humans at lower, more environmentally relevant dose levels. Still other chronic AACs are based on effects that are neither “irreversible” nor “incapacitating.”

As an example, the chronic AAC for acetophenone is based on an oral RfD, which in turn was derived based on “general toxicity” in rodents. Not only is the extrapolation based on oral toxicity data highly uncertain, but there was no effect in the study that served as the basis for the oral RfD that could be considered a serious irreversible or incapacitating effect. In fact, EPA’s Integrated Risk Information System (IRIS) database indicates that adverse effects were not observed even at the highest dose level of acetophenone tested (10,000 ppm in the diet); therefore, the highest dose level was considered a no-observed-adverse-effect level (NOAEL) and the RfD was set at a dose 3000 times lower than the NOAEL. As another example, the draft chronic AAC for vanadium is based on an oral RfD that was derived from a NOAEL for reduced hair cystine, which is neither a serious irreversible nor incapacitating effect, and the NOAEL was further reduced by an uncertainty factor of 100 to calculate the RfD. Acetophenone and vanadium are just two examples of chronic AACs that are inconsistent with the definition of adverse effects in the statute.

**Recommendation:** Toxicity criteria used to develop chronic AACs should be evaluated for scientific validity and consistency with the definition of adverse effects in the State statute. If these toxicity criteria do not meet the definition of “adverse effects,” as specified in the statute, the weight of scientific evidence should be considered, including relevant human data, to develop a more accurate value.

## **Toxicity criteria developed under other regulatory programs tend to overstate risks**

### **Application of uncertainty/variability factors in developing the non-cancer toxicity criteria**

The toxicity criteria developed for chronic non-cancer effects (e.g., RfCs, minimum risk levels [MRLs], Cal-EPA reference exposure levels [RELs]) are all derived using a similar methodology, which involves identifying the NOAEL or lowest-observed-adverse-effect level (LOAEL) in the most sensitive species and study. One of several uncertainty factors, generally 10-fold individually, is then applied to account for 1) the variation in sensitivity among members of the human population (intraspecies variability), 2) the uncertainty in extrapolating from animal data to humans (interspecies variability), 3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (e.g., extrapolating from subchronic to chronic exposure), 4) the uncertainty in extrapolating from a LOAEL to a NOAEL, and 5) the uncertainty associated with extrapolation from animal data when the database is incomplete. The combined uncertainty factor typically applied to derive the toxicity criteria ranges from 100 to 10,000. As a result of this practice, the toxicity criteria tend to greatly overestimate the actual likelihood of adverse effects and thus are typically well below any observed-effect levels based on scientific evidence. As discussed above, these types of levels are inconsistent with the statutory language concerning the levels that are to be used to determine the source category listing or whether a facility's emissions would produce adverse effects and therefore require HAPRACT.

In addition, although the Chronic AAC document implies that the AACs based on non-cancer effects were adjusted to a 30-year exposure period, no such adjustment is actually made because in the derivation equation the 30-year exposure period is divided by a 30-year averaging time thereby canceling out the 30-year adjustment. Because EPA RfCs and RfDs for example are protective for up to a lifetime of exposure, the resulting AACs assume lifetime exposure.

**Recommendation:** The toxicity criteria developed by EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), or the State of California are not always consistent with the definition of adverse effects described in the Arizona statute, because they serve different goals. Therefore, ADEQ should evaluate each criterion in the context of the statute and, when appropriate, assess the scientific literature, including relevant studies in humans (e.g., epidemiological and occupational studies), to develop levels above which adverse effects would be likely to occur in humans.

### **Use of a target risk of $1 \times 10^{-6}$ for carcinogens results in overly stringent chronic ambient air concentrations**

Chronic AACs are particularly low for those chemicals that are considered to be potentially carcinogenic (a designation based primarily on high-dose studies in animals). These extremely low chronic AACs (often below background) result from both conservative, worst-case assumptions relied upon as a part of the dose-response modeling (e.g., the response at high doses in animals is similar to anticipated responses in humans; there is no threshold for the response; the route and method of dose administration in the animal study is relevant for humans), and an inappropriately low target risk level.

In developing their air toxics programs, ADEQ selected a target cancer risk level of one in a million ( $1 \times 10^{-6}$ ) as their point of departure for calculating chronic AACs for all carcinogens. This is an unnecessarily conservative approach, because this risk level represents the lower end of the acceptable target risk range of one in a million to one in 10,000, as defined by EPA and other regulatory agencies, including ADEQ. Recently, in their proposed soil remediation level guidance, ADEQ stated that the site-specific remediation levels would result in “a level of contaminants remaining in the soil after remediation which results in a cumulative excess lifetime cancer risk between  $1 \times 10^{-6}$  and  $1 \times 10^{-4}$ .”

Additionally, as already discussed, the statute indicates that concentrations must be based on “adverse effects to human health” **that result in or significantly contribute to** an increase in mortality, serious irreversible illness, or incapacitating reversible illness. However, the lower

end of the acceptable risk range (i.e.,  $1 \times 10^{-6}$ ) does not define the upper limit above which chemical levels might be considered to be associated with such “adverse effects.” Rather, the target risk level represents a policy decision regarding an acceptable level of excess risk. In fact, there is no scientifically reliable evidence that exposure to a chemical at a level associated with a target risk level of  $1 \times 10^{-6}$  would result in an increase in mortality, serious irreversible illness, or incapacitating reversible illness, consistent with the State statute. From a practical standpoint, even large epidemiological studies would have difficulty distinguishing an increased risk of even  $1 \times 10^{-4}$ . Furthermore, a risk as low as  $1 \times 10^{-6}$ , in combination with the many worst-case and unrealistic assumptions used to estimate the cancer risk, results in chronic AACs that are below typical ambient concentrations for some commonly occurring chemicals (e.g., trichloroethylene, polycyclic aromatic hydrocarbons, formaldehyde, arsenic).

**Recommendation:** Given the lack of statutory support for a specific target risk level, ADEQ should choose a value that meets the public health goals of the statute (i.e., regulating emissions that result in adverse effects to human health and the environment), yet does not result in unnecessary listings. Unnecessary listings would include emissions of chemicals that, upon conducting a site-specific risk management analysis, would never result in risks exceeding the acceptable target risk range of  $1 \times 10^{-6}$  to  $1 \times 10^{-4}$ . The proposed chronic AACs and modeling of exposure concentrations are based on generic assumptions, with a high likelihood of overestimating exposure and toxicity. As a result, even a target risk of  $1 \times 10^{-5}$  or  $1 \times 10^{-4}$ , in many cases, would likely not be found to be associated with unacceptable risks in a site-specific risk management analysis, particularly if the scientific basis of the AAC is evaluated as well. In reality, even with a risk management level set at  $1 \times 10^{-4}$ , actual risks would be far lower, because even site-specific risk assessments retain several conservative assumptions to ensure that exposure and toxicity are not underestimated. As such, ADEQ should consider adopting a more reasonable target cancer risk level.



## Oral toxicity values may not be representative of inhalation risks

Review of Table 1 and associated footnotes in the Chronic AAC document indicates that the toxicity benchmarks for a number of the chronic AACs are based on an extrapolation from oral toxicity studies. Examples of specific HAPs whose toxicity benchmarks are based on extrapolation from oral studies include the following: acetophenone, antimony compounds, benzyl chloride, bis (2-ethylhexyl) phthalate, bromoform, chloroform, dibenzofurans, dichloromethane (methylene chloride), N,N-dimethylaniline, 2,4-dinitrotoluene, ethylene glycol, hexachlorobenzene, isophorone, methanol, phenol, polycyclic organic matter (surrogate-benzo(a)pyrene), polychlorinated biphenyls, selenium compounds, and 1,1,2,2-tetrachloroethane). Although it is reasonable to attempt to evaluate all chemicals regardless of the availability of inhalation toxicity values, application of toxicity values based on the oral route of administration is highly uncertain and may not be representative of inhalation risks. The state of the science clearly indicates that such extrapolation procedures ignore pharmacokinetic differences and are often scientifically invalid. In fact, several EPA guidance documents (e.g., U.S. EPA 1994, 1996), strongly discourage “across the board” route-to-route extrapolations like those done by EPA Regions 3 and 9 in developing their risk-based cleanup levels (RBCs) and preliminary remediation goals (PRGs). Route-to-route extrapolation can be highly uncertain and inaccurate when based exclusively on default assumptions regarding exposure and toxicokinetics, as done in developing the RBCs and PRGs.

For example, compared to inhalation exposure, oral exposure can result in either higher (i.e., administration of organic chemicals in a readily absorbed vehicle such as a solvent or corn oil) or lower absorption and toxicity (e.g., ingestion of elemental mercury). Oral administration studies are also inaccurate for characterizing inhalation toxicity when the lung is the site of injury. In addition, the active compound for many chemicals (e.g., chlorinated organic solvents) is often a metabolite that is produced in greatest amounts by the liver. Because of the first-pass effects, in which the liver receives absorbed substances directly from the gastrointestinal tract, intake via the oral route would result in a greater rate of metabolite formation and hence toxicity. This effect is most pronounced in oral dosing studies where chemicals are force fed in one bolus dose per day, rather than administered continuously as occurs with chronic inhalation

of a chemical in air or ingestion of a chemical in drinking water. Because chemicals are metabolized through different pathways, resulting in different metabolites depending on dose, bolus dosing may result in different effects and typically causes greater toxicity, particularly to the liver, than continuous administration.

Another example of a chronic AAC that is based on extrapolation from an oral study is antimony. In the study that serves as the basis of the inhalation toxicity value for antimony, rats were exposed to a single dose level of a soluble form of antimony administered in drinking water. No inhalation unit risk factor or RfC is available in the EPA IRIS file. Further, EPA has indicated that there is low confidence in the oral RfD. As such, use of the oral RfD as the basis for the chronic AAC is highly questionable. In contrast, however, EPA describes a study in a worker population exposed to antimony that suggests an inhalation NOAEL for myocardial damage of  $0.5 \text{ mg/m}^3$ . The latter may be a more appropriate basis for derivation of an inhalation-based AAC.

In considering the issue of route extrapolation, the EPA Region 9 reference cited by the Chronic AAC document indicates that:

Route-to-route extrapolations ("r") were frequently used when there were no toxicity values available for a given route of exposure. Oral cancer slope factors ("SFo") and reference doses ("RfDo") were used for both oral and inhaled exposures for organic compounds lacking inhalation values. Inhalation slope factors ("SFi") and inhalation reference doses ("RfDi") were used for both inhaled and oral exposures for organic compounds lacking oral values. Route extrapolations were not performed for inorganics due to portal of entry effects and known differences in absorption efficiency for the two routes of exposure. EPA Region 9 concludes by stating that whenever route-to-route extrapolation is used to calculate risk-based PRGs, additional uncertainties are introduced in the calculation.

In the U.S. EPA (1994) guidance document titled, *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*, criteria have been

established to inform decision-making regarding the appropriateness of extrapolating from one route of exposure to another. The EPA guidelines indicate that oral data should not be used for route-to-route extrapolation if any of the following criteria are met:

1. When groups of chemicals are expected to have different toxicity by the two routes (e.g., metals, irritants, and sensitizers)
2. When a first-pass effect by the respiratory tract is expected
3. When a first-pass effect by the liver is expected
4. When a respiratory-tract effect is established, but dosimetry comparison cannot be clearly established between the two routes
5. When the respiratory tract was not adequately studied in the oral studies
6. When short-term inhalation studies, dermal irritation studies, *in vitro* studies, or characteristics of the chemical indicate a potential for portal-of-entry effects at the respiratory tract, but the studies themselves are not adequate for development of an RfC.

**Recommendation:** Toxicity criteria based on extrapolation from oral studies should not be used to derive AACs unless such an extrapolation can be scientifically justified. The appropriateness of carrying out route-to-route extrapolation should be determined on a case-by-case basis and must account for the relationship between physicochemical properties, the absorption and distribution of toxicants, the significance of portal-of-entry effects, and the potential differences in metabolic pathways associated with the intensity and duration of exposure. Other toxicity criteria, such as scientifically valid human inhalation exposure studies, should also be considered

## Some toxicity criteria do not reflect the current state of the science

Some of the toxicity values available from EPA, ATSDR, and Cal-EPA may not reflect the current state of the science. Often, reviews and revisions are ongoing. Therefore, available values should not be used without determining whether those values are based on current science. For example, EPA recently indicated that the no-threshold, linear extrapolation of risk from high to low doses may not always be scientifically accurate, and that the mechanism of action of a chemical should be considered in assessing cancer risk. The examples below illustrate chemicals with AACs that are not based on the current state of the science or the most scientifically up-to-date regulatory values.

### Example: Trichloroethylene

The chronic AAC for trichloroethylene (TCE) is based on the upper end of a range of slope factors identified by EPA in their draft 2001 reassessment. This draft TCE slope factor is based on an epidemiological investigation of a population with oral exposure to TCE and other chemicals in drinking water. The draft EPA reassessment of TCE is under extensive review within EPA, following substantial comments from the EPA Science Advisory Board. As a result of the considerable uncertainty associated with the draft EPA toxicity values for TCE, some regulatory agencies (e.g., the New York Department of Health<sup>1</sup> and Cal-EPA) have elected to use alternative values. The New York Department of Health (NYDOH) considered the dose-response data for both carcinogenic and non-carcinogenic effects of TCE to derive an air guideline of  $5 \mu\text{g}/\text{m}^3$  for indoor air. NYDOH indicated that the study used by EPA to derive the upper-end provisional value did not provide an adequate basis for deriving a quantitative toxicity value. The Cal-EPA value is based on a group of inhalation studies that resulted in excess liver cancer in rodents. The Cal-EPA alternative toxicity value is identified in the EPA Region 9 PRG table as the "CAL modified PRG" of  $9.6 \times 10^{-1} \mu\text{g}/\text{m}^3$  ( $9.6 \times 10^{-4} \text{mg}/\text{m}^3$ ).

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<sup>1</sup> [http://www.health.state.ny.us/nysdoh/gas/svi\\_guidance/docs/kim\\_tceltr.pdf](http://www.health.state.ny.us/nysdoh/gas/svi_guidance/docs/kim_tceltr.pdf)

**Recommendation:** The slope factor used by the CAL modified PRG provides a more scientifically accurate basis for estimating inhalation cancer risks of trichloroethylene, because it was derived from inhalation studies and is more representative of health risks related to TCE (i.e., doesn't include exposures to other chemicals). However, before basing the chronic AAC on cancer, a full evaluation should be conducted of the toxicological and epidemiological data for this chemical to determine whether extrapolation of cancer risk to low doses is consistent with the State statute.

### **Example: Formaldehyde**

The chronic AAC for formaldehyde is based on a unit risk factor that was derived from high-dose studies in rodents. Such an approach is not justified, given the wealth of toxicology and epidemiology data in humans available from workplace, community, and controlled experimental studies (more than 22 experimental studies involving 500 individuals) as detailed in several recent comprehensive reviews (e.g., IARC 1995; Pasutenbach et al. 1997; ATSDR 1999; ACGIH 2001; Health Canada 2001; Bender 2002; WHO 2002; Liteplo and Meek 2003; NRC 2004).

The primary health effects associated with formaldehyde are related to the irritating and reactive properties of this highly water-soluble chemical. The most sensitive effects of formaldehyde at lower levels are thus related to irritation rather than cumulative systemic effects. Asthmatics are also not more sensitive at levels associated with upper respiratory irritation. In general, levels that do not produce short-term irritation also do not produce chronic irritation. Although exposures to concentrated formaldehyde solutions can result in allergic contact dermatitis, and inhalation of high airborne levels can result in bronchial spasms, a direct immunological basis for these reactions that is specific to formaldehyde appears to be lacking (IARC 1995; ATSDR 1999).

Based on controlled chamber studies, no difference in irritation effects is apparent between formaldehyde exposures around 0.5 ppm and below and clean air. A consistent dose-response relationship is more often observed at formaldehyde levels of around 1 ppm and above.

However, controlled chamber studies longer than 6 hours are unavailable. Less controlled studies, such as residential surveys and worker studies, provide supporting evidence, particularly for lower exposure levels and longer exposure times, but are of lower quality because of the lack of controls for many other factors that may underestimate the formaldehyde concentration associated with effects (e.g., background incidence of irritation, presence of other irritating chemicals, measurement accuracy both in terms of methodology and because peak exposure concentrations are often unmeasured or because air measurements were not taken at the time irritation was reported). Thus, although some of the less controlled studies indicate irritation at levels below 0.5 ppm, objective evidence is lacking that such effects would be caused by formaldehyde at these lower levels.

Consequently, despite all the human data for this chemical, a lower threshold for irritation in any and all persons for long-term exposures cannot be established by any one study, and such an exposure level would have to be based on a weight-of-evidence approach. The available human evidence indicates general concurrence in the literature, including occupational and community studies, that irritation effects would likely begin above 0.1 ppm, and that around this level, if any effects were to occur in sensitive people, these effects would be slight/mild and reversible, rather than annoying, and would certainly not be unbearable.

Formaldehyde has been considered to be carcinogenic via inhalation by EPA based on high-dose inhalation studies in animals (EPA IRIS record last revised in 1991). However, the weight of current scientific evidence indicates that cancers in rodents exposed repeatedly over time to high doses (e.g., typically 10–15 ppm) of formaldehyde occur by a mechanism that is irrelevant for low doses (i.e., cell necrosis and regenerative hyperplasia resulting in increased cell replication and thereby increased potential for malignant cells to occur). The primary concern for cancer is thus at doses that result in tissue damage. In humans, the overall evidence for cancer is inconsistent, and associations are relatively weak when statistically significant (IARC 1995; Collins et al. 1997; ATSDR 1999; Marsh et al. 2002; Coggon et al. 2003; Hauptmann et al. 2003, 2004; Pinkerton et al. 2004).

EPA is currently reviewing its unit risk factor for formaldehyde, which at present, is based on high-to-low-dose extrapolation from the animal data. Specifically, EPA is considering a biologically motivated, two-stage carcinogenicity model developed by CIIT (1999) that was externally peer reviewed by Health Canada and EPA (Health Canada and EPA 1998). This model results in different dose-response relationships at high doses versus low doses. At high doses, the model is driven primarily by cytotoxicity and regenerative hyperplasia, whereas at low doses, a much shallower slope is determined largely by genotoxicity data on formaldehyde, conservatively assuming that the risk of cancer is related to one marker of genotoxicity, DNA-protein cross-link formation, although this relationship has not been established.

Research and analysis related to CIIT (1999) is being published in separate papers (Conolly et al. 2003, 2004; Gaylor et al. 2004). The two-stage carcinogenicity model has been relied upon by WHO (2002) and Health Canada (2001) in their risk assessments of inhaled formaldehyde. Based on the results of this model, background air levels of formaldehyde would be associated with a risk well below one in a million. Continuous exposure to an air level as high as 0.3 ppm (the occupational exposure limit) is associated with a lifetime risk of 1 in 10 million in non-smokers and three in a million for smokers (CIIT 1999; NRC 2004). Connolly et al. (2004) conclude “that cancer risks associated with inhaled formaldehyde are de minimis ( $10^{-6}$  or less) at relevant human exposure levels, and (2) protection from the noncancer effects of formaldehyde should be sufficient to protect from its potential carcinogenic effects.” Clearly, chronic risks at low doses should be based on preventing irritation and related complications. Exposures that are protective of such effects would have a negligible risk of cancer.

**Recommendation:** Low-level environmental exposures with no significant irritation and irreversible changes in nasal mucosa would also be protective of cancer. This should be the focus for AAC development.

### **Example: Chloroform**

The Chronic AAC document indicates that the AAC for chloroform is based on a unit risk factor (URF) of 2.3E-02 available on IRIS. However, there is no such value currently available in

IRIS. In fact, IRIS no longer includes an inhalation URF for this compound. In 2001, EPA made a fundamental change in the way they assessed the carcinogenic risk for chloroform. In contrast to the traditional approach employed by EPA for deriving cancer potency values, wherein the response is assumed to be linear when extrapolating from the high doses in animal studies to the lower doses to which humans are likely to be exposed, EPA has now adopted a margin-of-exposure approach based on their new cancer risk guidelines. These guidelines allow recognition of the mode of action for carcinogenicity.

The available data indicate that chloroform is not strongly mutagenic and is not expected to produce rodent tumors via a mutagenic mode of action at low doses (ILSI 1997). The scientific literature indicates that the carcinogenic responses and tumor formation observed in animals are associated with regenerative hyperplasia (i.e., excess cellular multiplication and tissue growth) that occurs in response to cytolethality (killing of cells by direct high-dose toxicity; ILSI 1997; U.S. EPA 2001). Because cytolethality occurs only at exposure levels above some critical dose level, EPA has concluded that a nonlinear approach is the most appropriate method for characterizing the cancer risk from chloroform.

The EPA *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA 2005a) discusses the interpretation of carcinogenicity data from studies where cancer is observed only following “excessive doses” and indicates that: “Studies that show tumor effects only at excessive doses may be compromised and may or may not carry weight depending on the interpretation in the context of other study results and other lines of evidence. Results of such studies, however, are generally not considered suitable for dose-response extrapolation if it is determined the mode(s) of action underlying the tumorigenic responses at high dose is not operative at lower doses.”<sup>2</sup> For chloroform, available evidence indicates that chloroform-induced carcinogenicity is secondary to cytotoxicity and regenerative hyperplasia. As such, U.S. EPA (2001) now relies on a nonlinear dose-response approach and margin-of-exposure analysis to characterize the cancer risk for ingested chloroform. Because the mode of action indicates that cytotoxicity is the critical effect, EPA has concluded that the RfD would be protective of both carcinogenic and

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<sup>2</sup> <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283>



noncarcinogenic effects. EPA's assessment of the oral toxicity of chloroform was finalized in October of 2001 and is described in the IRIS database.

EPA has yet to derive an RfC, and the current EPA IRIS file does not include an inhalation value. The Chronic ACC appears to draw from the EPA Region 9 value, which is apparently the former oral unit risk factor based on liver cancer in mice resulting from administered chloroform by oral gavage (bolus dosing). As noted for the oral carcinogenicity and RfD assessment, the mechanism by which such cancer would occur (cytotoxicity) is not relevant for lower doses and would be even more inappropriate for evaluating inhalation exposures in which the first-pass effect through the liver would not occur.

**Recommendation:** Given the importance of the underlying toxicity criteria used to develop AACs, it is important that all values be verified as accurate according to the scientific literature. While the EPA Region 3 and Region 9 RBC and PRG tables still indicate that there is a URF available on IRIS for chloroform, these sources are out of date. Additionally, evidence of cancer at high doses, as indicated by cellular necrosis and regenerative hyperplasia, cannot be extrapolated to lower doses at which such effects would not occur. Several other chemicals have also been found to act by similar mechanisms at high doses (e.g., ethylene dibromide, formaldehyde). The validity of low-dose extrapolation of cancer risk for these chemicals should be evaluated as well.

### **Some of the chronic AACs are based on highly uncertain toxicity values**

In some cases, the chronic AACs are based on provisional peer-reviewed toxicity values (identified as "PPRTVs" in the footnotes to Table 1 in the Chronic AAC document). These values, derived by EPA Superfund Technical Support Center staff, are not included in IRIS, and are not readily available for public review, but rather are provided to EPA Regional Risk Assessors for use in addressing chemicals detected at specific sites. The PPRTVs are not intended to be used broadly across programs. These values have not undergone a comprehensive peer-review, and many are highly uncertain. The PPRTVs are often based on a default route-to-route extrapolation and/or on surrogate data (i.e., data for another compound

that is believed to be structurally similar). Examples of chronic AACs that are based on these highly uncertain provisional toxicity values include cobalt compounds and 1,1,1-trichloroethane (methyl chloroform). In some cases, it may actually be more appropriate to evaluate toxicity values derived by other agencies (e.g., ATSDR, Cal-EPA), because these values are subjected to more extensive review and are typically described in detailed background documents. As such, these toxicity values are likely to be more scientifically sound and transparent to the public and regulated entities.

**Recommendation:** ADEQ should review the scientific literature, including relevant human studies (e.g., occupational and epidemiological values) to determine whether the provisional toxicity values are scientifically sound and can be used in the desired application.

### **More information is needed concerning the flow chart for selection of chronic AACs (Figure 1 in the Chronic AAC document by ADEQ)**

Figure 1 in the Chronic AAC document indicates that, for Tier 2, the chronic AACs based on EPA Region 3 RBCs or Region 9 PRGs are compared to other criteria (e.g., MRLs, Cal-EPA RELs) to determine if there is “reasonable agreement”. If there is not, then, as indicated in the flow chart, the next step is to review the basis of the criterion and then to select the most appropriate criterion. Given some of the limitations inherent in many of the RBCs and PRGs (e.g., default route-to-route extrapolations; inclusion of provisional toxicity values), this is clearly an important step. More information is needed to understand what constitutes “reasonable agreement,” as well as how the criterion was reviewed in cases where there was not reasonable agreement. For example, for cobalt compounds, the chronic AAC is based on the ambient air PRG of  $6.86 \times 10^{-7}$  from EPA Region 9. As indicated above, this ambient air PRG is based on a provisional toxicity value. In contrast, the ATSDR MRL is  $1.04 \times 10^{-4}$ , about three orders of magnitude less conservative than the PRG. This represents a substantial difference. Given these highly divergent numbers, it is critical that the chronic AAC selected is based on sound scientific rationale rather than always selecting one agency value over another without evaluation of the underlying scientific basis of each value.

**Recommendation:** ADEQ should provide more detailed information concerning how the criteria are reviewed, as well as describe the process for selecting the most appropriate value. Ideally, documentation should be provided for each individual HAP that is subject to such a review. This is critical if the process for establishing chronic AACs is to be completely transparent and open.

### **Several of the chronic health-based concentrations are below levels typically found in ambient air**

A preliminary comparison of the chronic AACs to readily available background concentration data indicates that many of the AACs are within or below background air concentrations experienced by large population (urban) centers. Specifically, some of the chronic AACs are set at levels that are either near concentrations typically detected in background air, or are, in some cases, are nearly 400 times lower than background. Many of the substances with levels below background are based on the very stringent target cancer risk of one in a million. Metals occur naturally in soil, dust, and air. In urban settings, various sources (e.g., swimming pools, consumer products, building materials, automobiles, wood stoves) emit low-level, detectable concentrations of chemicals to indoor and outdoor air. Table 1 provides a comparison of the chronic AACs to concentrations in urban ambient air where no known source is present, as identified in reviews prepared by ATSDR. While these typical ambient air levels are variable, and it is uncertain how directly applicable they are for the regulated areas under consideration in Arizona, they do indicate that the chronic AACs are well below typical ambient concentrations in several cases. Consequently, it appears unreasonable to assume that serious irreversible effects would occur at levels below background levels, particularly for naturally occurring substances.

**Recommendation:** We recommend that, as a reality check, ADEQ compare all AACs to relevant background concentrations as a part of assessing whether the levels would define exposures above which adverse effects would occur, as defined by the State statute.

## **The worst-case surrogate compound is used to represent a group of related chemicals**

### **Example: Chromium Compounds**

The chronic AAC for chromium compounds is based on the URF for chromium (VI). EPA derived a Cr(VI) unit risk of  $12 \text{ (mg/m}^3\text{)}^{-1}$  based on an elevated incidence of lung cancer in a cohort of Painesville, Ohio, chromate production workers who were exposed to soluble and insoluble chromium over many years in the workplace (U.S. EPA 2005b; Mancuso 1975, 1997). The Chronic AAC document, however, appears to imply that the chronic AAC of  $1.58 \times 10^{-7} \text{ mg/m}^3$ , calculated using the Cr(VI) unit risk factor, should be applied to total chromium. Although this is consistent with the approach taken by EPA Region 9 in calculating their ambient air PRG for total chromium, it is scientifically incorrect. EPA Region 9 also derives a Cr(VI) ambient air PRG by further adjusting the EPA unit risk by a factor of 7, under the assumption that the ratio of Cr(III) to Cr(VI) at the Painesville, Ohio, chromate production plant was 6:1, based on samples of soluble and insoluble total chromium. However, ample evidence suggests that not only is the EPA Region 9 adjustment in error, but the EPA slope factor actually overestimates Cr(VI) risk as well:

- Many researchers have questioned the reliability of the 6:1 ratio in the past (Proctor et al. 1999; Gibb and Chen 1986), and new data from the plant indicate clearly that this ratio is in error (Proctor et al. 2003). Mancuso (1975, 1997) measured water-soluble and acid-soluble chromium and assumed that the former was primarily Cr(VI) and the latter Cr(III). In fact, both Cr(III) and Cr(VI) can be present in water- or acid-soluble forms. Research conducted to reconstruct past Cr(VI) exposures experienced by the Mancuso (1975, 1997) cohort suggests that Cr(VI) concentrations identified in Mancuso (1975, 1997) likely represent lower-bound estimates (Proctor et al. 2003). Specifically, data compiled by Proctor et al. (2003) indicated higher Cr(VI) concentrations than had been determined previously for acid-soluble chromium in many of the plant areas. In fact, the chromium to which

many workers were exposed was almost 100% Cr(VI). The underestimation of the relative proportion of Cr(VI) would cause an overestimate of risk.

- The chromium concentrations used by Mancuso (1975, 1997) were collected in 1949, many years after actual exposures occurred in the 1930s. These concentrations likely underestimate the exposure levels actually experienced by the workers in the study. Newly identified data (Proctor et al. 2004) from the Painesville plant clearly indicate that exposures were higher prior to 1949, when the airborne chromium samples were collected. Record reviews and interviews with former workers support this assumption and indicate that exposures were likely higher during the 1930s when plant conditions were extremely dusty (Proctor et al. 2003). Underestimation of the dose in the relevant epidemiological study would have the effect of overestimating chromium risks (i.e., attribution of observed risks to a lower dose increases apparent toxicity).
- The Mancuso (1975, 1997) studies did not include information on smoking history. In the absence of smoking history data, EPA's analyses assumed that smoking prevalence was consistent with that of the general population. However, as EPA acknowledges in their Cr(VI) toxicology profile<sup>3</sup>, smoking prevalence is generally considered to be much higher within industrial cohorts. Given the clear contribution of smoking to lung cancer, and the apparent underestimate of smoking prevalence in the study population, lung cancer risk attributed to Cr(VI) exposure would thus be overestimated.

Based on a detailed analysis and subsequent reanalysis of the Mancuso (1975, 1997) studies by Proctor and colleagues (2003), it is clear that EPA Region 9's adjustment of the Cr(VI) unit risk is in error. The EPA unit risk of  $12 \text{ (mg/m}^3\text{)}^{-1}$  is meant to be applied to Cr(VI), without adjustment, and in fact, likely overestimates Cr(VI) risk itself. Because total chromium could be 100% Cr(III), 100% Cr(VI), or any mixture in between, it is not meaningful to set a total chromium concentration based on an assumed ratio of the two in air. Furthermore, application

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<sup>3</sup> <http://www.epa.gov/iris/toxreviews/0144-tr.pdf>

of the 6:1 ratio has no basis. As discussed above, the assumed 6:1 ratio for workplace air in the Mancuso (1975, 1997) was likely an incorrect underestimate of relative Cr(VI) concentrations. In addition, even if one were to assume that the ratio was correct for the Painesville chromate plant, that ratio is irrelevant for ambient air.

**Recommendation:** Eliminate the proposed “chromium compounds” chronic ambient air concentration. Apply the proposed “chromium compounds” chronic ambient air concentration, based on the EPA unit risk of  $12 \text{ (mg/m}^3\text{)}^{-1}$ , to Cr(VI) only. Consider whether the epidemiological data would even support that cancer would result at low ambient levels. Do not derive an additional chronic ambient air concentration for Cr(III), because this essential element is relatively non-toxic, and there are inadequate data on the effects of inhaled Cr(III) (U.S. EPA 2005b).

### **Example: Polycyclic Organic Matter**

The AAC for polycyclic organic matter (polycyclic aromatic hydrocarbons; PAHs) is based on the oral slope factor for the most carcinogenic member of this group, benzo[a]pyrene. However, not all of the PAH compounds are considered by EPA to be carcinogenic. Even for those with the potential to be carcinogenic based on animal studies, adjustment factors have been developed by EPA to reduce the benzo[a]pyrene slope factor for these less carcinogenic PAHs. For example, EPA Region 9 provides separate PRGs for each of the seven PAHs considered to be carcinogenic (benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, chrysene, dibenz[ah]anthracene, and indeno[1,2,3-cd]pyrene), as well as for six noncarcinogenic PAHs (acenaphthene, anthracene, fluoranthene, fluorene, naphthalene, and pyrene). The PAHs vary considerably in their toxicity, and as a result, the EPA Region 9 PRGs vary from the lowest PRG of  $0.00092 \text{ } \mu\text{g/m}^3$  for the carcinogenic benzo[a]pyrene and dibenz[ah]anthracene to the highest value of  $1095.0 \text{ } \mu\text{g/m}^3$  for anthracene, which was derived by EPA Region 9 based on the EPA oral RfD for anthracene. Therefore, considering all PAHs to be as carcinogenic as benzo[a]pyrene is not supported by the available scientific evidence, nor by the regulatory practices of other agencies. These regulatory examples are provided to demonstrate the lack of necessity to consider all PAHs to be as toxic as the worst-case surrogate.

Development of an AAC, of course, should consider the scientific data for each PAH compound, and take into account our previous comments on route-to-route and animal to human extrapolations and use of a low target cancer risk level.

**Recommendation:** Develop AACs for each PAH compound based on the scientific evidence for its specific toxicity. In applying this approach, there is still considerable uncertainty related to the fact that only one of the PAHs, naphthalene, has an inhalation-based toxicity value. The remaining PAHs are all based on oral toxicity values. Thus, the underlying oral toxicity data should be reviewed to assess whether route-to-route extrapolation may be justified for derivation of inhalation ACCs.

### **Example: Arsenic and Arsenic Compounds**

Arsenic and arsenic compounds may include arsine gas, according to comments by ADEQ at a recent public and stakeholder meeting. However, arsine gas differs greatly in toxicity from particulate forms of arsenic. Arsine gas is more acutely toxic and causes different health effects (e.g., red blood cell hemolysis) than particulate arsenic compounds, but is not considered to be carcinogenic with chronic exposure. Even among arsenic compounds, lung cancer has been associated with high-dose exposures to arsenic trioxide in historical smelter workers but not with exposures to other forms of arsenic, such as sulfide forms in ore from mining.

**Recommendation:** Develop separate AACs for different arsenic forms based on the scientific weight of evidence supporting their toxicity.

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**Table 1. Chronic air concentrations compared with typical air concentrations**

Chemical	Proposed AAC	Typical Ambient Air Concentration	Ratio of Typical Air Concentrations to AAC	Notes on Typical Air Concentrations
Arsenic	4.41E-07	1.50E-06	3.4	CARB mean
	4.41E-07	4.20E-06	10	ATSDR outdoor air low mean Great Lakes urban
	4.41E-07	9.60E-06	22	ATSDR outdoor air high mean Great Lakes urban
Beryllium	7.90E-07	Undetectable at 3E-08	NA	ATSDR report that "most" EPA Storage and Retrieval of Aerometric Data Database Stations are undetectable
	7.90E-07	2.00E-08	0.03	ATSDR outdoor Detroit air low mean
	7.90E-07	2.00E-06	2.5	ATSDR outdoor Detroit air high mean
Benzene	2.43E-04	1.56E-02	64.1	ATSDR outdoor air low median
	2.43E-04	1.14E-01	467.7	ATSDR outdoor air high median
	2.43E-04	5.84E-03	24.1	ATSDR suburban outdoor air daily median
Cadmium	1.06E-06	1.00E-06	0.94	ATSDR outdoor air mean remote locations
	1.06E-06	3.00E-06	2.8	ATSDR outdoor urban air low mean
	1.06E-06	4.00E-05	37.7	ATSDR outdoor urban air high mean
Chromium	1.58E-07	3.90E-06	24.7	California (CARB) mean
	1.58E-07	1.20E-06	7.6	ATSDR chromium(VI) background mean rural New Jersey
	1.58E-07	1.00E-05	63.3	Total chromium - ATSDR outdoor urban air low
	1.58E-07	3.00E-05	189.9	Total chromium - ATSDR outdoor urban air high
Ethylene dichloride	7.29E-05	Undetected	NA	ATSDR outdoor rural, suburban air
	7.29E-05	4.90E-05	0.7	ATSDR outdoor urban air median
Formaldehyde <sup>a</sup>	3.16E-04	2.50E-03	7.9	ATSDR outdoor urban air median
	3.16E-04	1.00E-03	3.2	ATSDR outdoor rural and urban air low
	3.16E-04	6.80E-02	215.2	ATSDR outdoor rural and urban air high
	3.16E-04	7.60E-02	240.5	ATSDR indoor air newly constructed conventional
	3.16E-04	5.00E-02	158.2	ATSDR indoor - older conventional home high
TCE	1.68E-05	2.51E-03	149.5	ATSDR urban/suburban outdoor mean
	1.68E-05	4.50E-03	268.0	EPA background mean in indoor air

**Note:** Concentrations are reported in mg/m<sup>3</sup>.

ADEQ - Arizona Department of Environmental Quality  
 ATSDR - Agency for Toxic Substances and Disease Registry  
 CARB - California Air Resources Board

EPA - U.S. Environmental Protection Agency  
 NA - not available

<sup>a</sup> Background levels from mobile homes were not included because the levels are considerably higher as a result of the homes' construction.